100812-55-3; **14**, 100812-56-4; **14a**, 100812-57-5; **14b**, 100812-58-6; **14c**, 100812-59-7; **15**, 100812-60-0; **15a**, 100812-61-1; **15b**, 100812-62-2; **15c**, 100812-63-3; **16**, 100812-64-4; **16a**, 100812-65-5; **16b**, 100812-66-6; **16c**, 100812-67-7; **17**, 100812-68-8; **17a**, 100812-69-9; **17c**, 100812-70-2; **18**, 100812-71-3; **18a**, 59463-21-7; **18c**, 59463-14-8; **19**, 100812-72-4; **19a**, 100812-73-5; **19b**, 100812-74-6; **19c**, 100812-75-7; **20**, 100812-76-8; **20a**, 100812-77-9; **20b**, 100812-78-0; **20c**, 100812-79-1; **21**, 100812-80-4; **21a**, 59463-21-7; **21b**, 100812-81-5; **21c**, 100812-82-6; **22**, 100812-83-7; **22a**, 100812-84-8; **22b**, 100812-85-9; **22c**, 100812-86-0; **23**, 100812-87-1; **23b**, 100812-88-2; **23c**, 100812-89-3; **24**, 100812-90-6; **24a**, 100812-91-7; **24b**, 100812-92-8; **24c**, 100812-93-9; **25**, 81302-80-9; **26**, 80121-73-9; **27**, 100812-94-0; **28**, 87603-80-3; **29**, 100812-95-1; **30**, 100812-96-2; **31**, 100812-97-3; **32**, 100812-98-4; **33**, 100812-99-5; **34**, 100813-00-1; **35**, 100813-01-2; **36**, 100813-02-3; 2-formyldithiane, 34906-12-2; triethyl phosphonoacetate, 867-13-0; diethyl (cyanomethyl)phosphonate, 2537-48-6; 1-(triphenylphosphoranylidene)-2-propanone, 1439-36-7; diethyl [(*N*,*N*-diethylcarbamoyl)methyl]phosphonate, 3699-76-1; 3-(trimethylsilyl)-2-methylenepropyl vinyl ether, 87603-79-0; 3-ethoxy-2-cyclohexen-1-one, 5323-87-5; 3-ethoxy-5-methyl-2-cyclohexen-1-one, 35023-83-7; 3-ethoxy-2-methyl-2-cyclohexen-1-one, 20643-20-3; 3-ethoxy-2,6-dimethyl-2-cyclohexen-1-one, 76192-88-6; 3-ethoxy-1,2-dimethyl-6-[2-[(trimethylsilyl)methyl]allyl]-2-cyclohexen-1-ol, 100813-03-4; 3-ethoxy-2-cyclopenten-1-one, 22627-70-9; 3-ethoxy-5-methyl-2-cyclopenten-1-one, 100813-04-5; 3-ethoxy-2-methyl-2-cyclopenten-1-one, 25112-86-1; 3-ethoxy-2,5-dimethyl-2-cyclopenten-1-one, 100813-05-6.

Selective Reduction of Cyclic Conjugate Enones with $NaBH_4$ in the Presence of Cyclodextrins[1]

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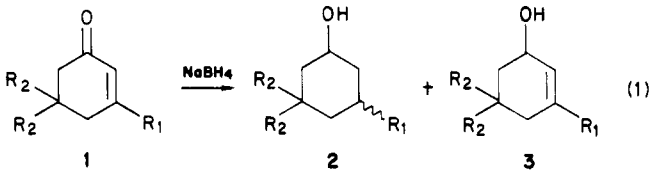
The $NaBH_4$ reduction of 2-cyclohexenone (**1a**), 3-methyl-2-cyclohexenone (**1b**), and 3,5,5-trimethyl-2-cyclohexenone (**1c**) to the corresponding cyclohexanols (**2**) and cyclohexenols (**3**) has been investigated in aqueous alkaline media, in the absence and in the presence of α- and β-cyclodextrins (CD) and two modified β-CDs. Changes in the [**2**]/[**3**] ratios are induced by substrate inclusion in the CD's cavities. The reduction (**1b**) is accelerated in the presence of β-CD. The strength and mode of substrate insertion into the CD's cavities have been inferred from a ^1H NMR spectroscopy investigation. The formation of a ternary complex made of CD, substrate, and boron hydride species is suggested to account for the observed selectivities.

Cyclodextrins (CDs), doughnut-shaped macrocycles composed of six or more glucose units, have been extensively investigated as simple enzyme models owing to their ability to form inclusion complexes with a variety of substrates.[2] High rate accelerations have been observed for the hydrolytic cleavage of activated substrates.[3] More recently, inclusion complexes have been reported to undergo selective reactions.[4-7] The common feature of these reactions is the critical dependance on the geometry of the complexes which can be modulated by modifying both the guest and host molecules.

We report herewith the selectivity effects, resulting from CD inclusion, in the $NaBH_4$ reduction of α,β-unsaturated cyclic ketones **1a–c**. These are known[8] to undergo a $NaBH_4$ reduction to give the corresponding alkanols (**2**) or alkenols (**3**) (eq 1), formally related to a hydride attack



(1)

a, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = R_2 = CH_3$

at C_3 or C_1, the product ratio depending on the reagent structures or reaction conditions.[9]

The study of regioselectivity effects in the presence of α- and β-CD and also, in the case of enone **1b**, in the presence of two modified β-CDs, i.e., heptakis(2,6-di-*O*-methyl)-β-CD and heptakis(6-*N*-methyl-*N*-acetyl)-β-CD, has been complemented by a NMR spectroscopy investigation aimed at defining the mode of inclusion of the substrates in the CD complexes and the strength of binding.

Results

Selective Reduction of Cyclohexenones 1a–c in the Presence of CDs. Table I shows the cyclohexanol (**2**)/cyclohexenol (**3**) mole ratios observed in the reduction products for aqueous 0.2 M Na_2CO_3 solutions using different CD/substrate ratios. The table also includes an indication of the fraction of bound substrate as evaluated from the binding constants, K_b, determined by NMR measurements (see below).

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Table I. Product Ratios, [2]/[3] × 10 (at the CD/1 Mole Ratios[a] and Estimated % of Bound Substrate[b] Indicated), in the Reduction of Cyclohexenones 1a–c by $NaBH_4$ in the Presence and Absence of CD's and Their Derivatives

1a		1b				1c	
α-CD	β-CD	α-CD	β-CD	2,6-OMe[c]	6-NMeAc[d]	α-CD	β-CD
6.35 (0)			1.28 (0)[e]			29.0 (0)	
6.65 (1; 4.4)	11.4 (1; 18.8)	1.05 (1; 4.0)	2.32 (1; 16.8)	2.10 (1)	2.1 (1)	27.5 (1.4; 4.1)	18.1 (1.8; 37.1)
7.73 (5; 18.7)	14.6 (2; 31.2)	0.94 (5; 17.1)	3.90 (2; 28.3)	4.72 (5)	2.95 (2)	24.9 (4.9; 13.1)	12.8 (5.5; 62.9)
8.25 (10; 31.4)	20.9 (6; 56.4)	0.81 (10; 29.0)	5.34 (4; 43.5)	5.08 (10)	4.1 (4)	24.5 (9.4; 22.5)	11.7 (9.8; 74.5)
			6.70[f] (7; 56.7)		5.0 (8)	24.1 (16.7; 33.9)	11.4 (16.2; 82.5)
			6.80 (9; 62.5)				

[a] First number in parentheses. [b] Second number in parentheses. [c] Heptakis(2,6-*O*-methyl)-β-CD. [d] Heptakis(6-*N*-methyl-*N*-acetyl)-β-CD. [e] 1.25 in the presence of α-methyl glucoside in a 40-fold molar excess (CD absent). [f] Values with added benzoic acid (at the mole ratio [benzoic acid]:[**1b**] indicated in parentheses): 5.6 (1); 4.13 (7); 2.64 (15).

Table II. Initial Rates for the Disapperance of 1b[a,b] and the Formation of 2b and 3b in the Presence and in the Absence of β-CD

mole ratio β-CD/1	initial rate of disappearance of **1b**, (mol·L^{-1}·s^{-1}) × 10^8	initial rate of formation, (mol·L^{-1}·sec^{-1}) × 10^8	
		2b	**3b**
0	8.3 ± 0.4	0.85 ± 0.1	7.5 ± 0.2
7	12.9 ± 0.4	5.0 ± 0.2	7.4 ± 0.2

[a] Charged amount: **1b**, 0.045 mmol; $NaBH_4$, 0.13 mmol; β-CD, 0.32 mmol. [b] In 20 mL of 0.2 M Na_2CO_3.

The selectivity effects are in each case more pronounced in the presence of β- than in the presence of α-CD. With both CDs, on going from cyclohexenone **1a** to **1b** and **1c**, a relative shift of the hydride attack position from the unsaturated C_3 (yielding **2**) to the carbonyl C_1 (yielding **3**) is observed. Thus, in the case of **1a** the [**2**]/[**3**] ratio increases and in the case of **1c** the ratio decreases with both CDs; enone **1b** is a borderline substrate: the [**2**]/[**3**] ratio decreases with α- and increases with β-CD.

The absence of any effect in the reduction of **1b** in the presence of methyl glucoside as well as the inhibition observed by addition of increasing amounts of benzoic acid to a β-CD solution clearly indicate that the formation of an inclusion complex is a prerequisite to the selectivity effects. Moreover, at least in the case of **1b**, the effects of the modified β-CDs, where the hydroxyl groups at the 2 and 6 positions, (2,6-OMe), and at the 6 positions, (6-NMeAc), are substituted, are virtually identical although slightly less pronounced than those observed with the unmodified β-CD: this apparently rules out any substantial involvement of the CD's hydroxyl functions in the selective reduction.

Rate Measurements. Kinetic experiments were carried out by VPC analysis to measure the rate of disappearance of **1b** and those of formation of **2b** and **3b** in the presence and absence of β-CD. Under identical conditions (0.2 M Na_2CO_3, 25 °C), as shown from data reported in Table II the disappearance of **1b** is 1.5 times faster in the presence than in the absence of β-CD and, quite interestingly, the increase is totally accounted for by the accelerated formation of the anol **2b**; the rate of formation of **3b** is, in fact, the same, within the experimental error, with and without β-CD.

These kinetic results are also consistent with the finding that a plot of the [**2b**]/[**3b**] ratio vs. the mole fraction ([CD·**1b**]/[**1b**]$_0$) of complexed **1b** is linear (see Figure 1). Since the above ratio is given[10] by eq 2,

$$[2]/[3] = \frac{k_2^f + \Delta k_2[\mathrm{CD}\cdot 1]/[1]_0}{k_3^f + \Delta k_3[\mathrm{CD}\cdot 1]/[1]_0} \qquad (2)$$

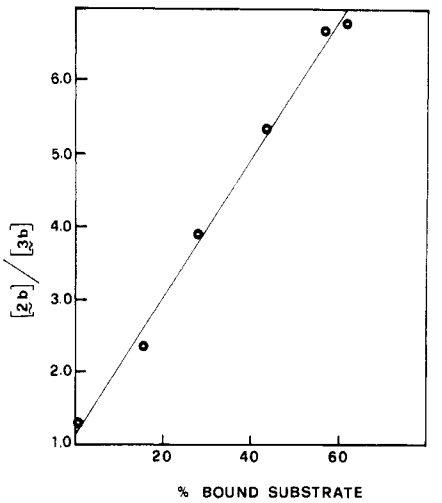

Figure 1. Linear plot of the 3-methylcyclohexan-1-ols (**2b**)/3-methyl-2-cyclohexen-1-ol (**3b**) ratio vs. % bound 3-methyl-2-cyclohexen-1-one (**1b**) in β-CD.

where k_2^f and k_3^f are the rate constants for the formation of **2** and **3** from the uncomplexed substrate and Δk_2 and Δk_3 are the rate constant differences for the formation from the complexed and uncomplexed substrates, a linear slope is verified when $\Delta k_3 \approx 0$, as observed. This also allows one to estimate an increase in the rate of alkanol formation by a factor of 9.5 when the substrate is 100% bound to β-CD.

^{1}H NMR Measurements. Binding constants K_b and induced chemical shift changes ν_c in the substrate protons were measured with a 200-MHz spectrometer for D_2O solutions of cycloalkenones **1a–c** in the presence of α- and β-CD. The concentration $[1]_0$ of the substrate was kept constant, and its resonances were monitored with reference to Me_2SO as the internal standard[12] against increasing

(10) Equation 2 assumes that the same mechanism leads to products in the reduction of both the complexed and the uncomplexed substrates. This cannot be taken for granted since there are doubts concerning the actual reducing species in the $NaBH_4$ reduction of ketones.[19] However the [**2b**]/[**3b**] ratios measured at different interval times during a single run, both in the presence and absence of β-CD, were constant within the experimental error, a slight decrease (less than 10%) being observed after at least 90% of the ketone was reduced.[11] Moreover, the formation of **2a**, being a two-step process, likely involves the formation of 3-methylhexanone and equation 2 requires that its reduction is a fast process and the hydride attack at C_3 is the rate-determining step. This is indeed the case since the above intermediate was sought but never detected among the products during the reduction of **1b**.

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(12) We chose Me_2SO due to its very low K_b (0.37 M^{-1}) with α-CD (see Gelb, R. I.; Schwartz, L. M.; Radeos, M.; Edmonds, R. B.; Laufer, D. A. *J. Am. Chem. Soc.* **1982**, *104*, 6283) and the stability of its signal under the experimental conditions.

Table III. Binding Constants, K_b (M^{-1}), and Calculated Proton Shifts, ν_c[a] (Hz), for Fully Complexed Enones 1a–c

substrate	CD	ν_c, position[b] 2	3	4	5	6	K_b[c] average, M^{-1}
1a	α	45.9	18.0	25.2	24.2	26.7	22.3 ± 1.5
	β	10.0	6.5	16.4	16.0	1.6	141.5 ± 1.0
1b	α	68.0	27.3	29.0[d]	32.2	29.0[d]	19.3 ± 2.1
	β	9.9	21.4	14.9	16.4	−9.1	120.6 ± 7.2
1c	α	77.8	30.1	30.7	47.1	27.2	32.3 ± 7.5
	β	26.2	21.1	7.6	20.1	1.2	621.9 ± 9.7

[a] Positive values refer to downfield shifts. For the determination of ν_c see Experimental Section. [b] For the groups linked to the corresponding position in the ring. [c] See Experimental Section. [d] Signals always coincident.

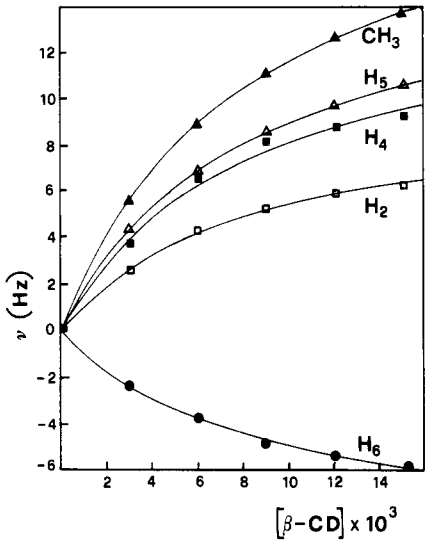


Figure 2. Chemical shift changes experienced from the different protons of **1b** ($[1b]_0 = 1.76 \times 10^{-4}$ M) with increasing amounts of added β-CD (D_2O, 25 °C). Solid lines represent computer-calculated curves assuming $K_b = 120.6$ M^{-1}.

concentrations, $[CD]_0$, of CD. Under the condition $[CD]_0 \geq 10 \times [1]_0$ eq 3 applies:

$$\nu = \frac{\nu_c K_b [CD]_0}{1 + K_b [CD]_0} \quad (3)$$

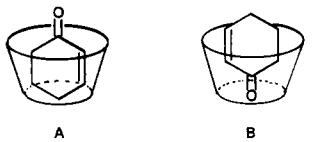
where ν is the observed change in the chemical shift of a given substrate proton relative to that in the absence of CD and ν_c is the limiting chemical shift change for the fully complexed substrate. Figure 2 shows the $\nu - [\beta\text{-CD}]$ profiles observed in the case of **1b**. Using equation 3 in the reciprocal form, plots of $1/\nu$ vs. $1/[CD]_0$ allows the evaluation of K_b and ν_c (see also the Experimental Section).

Table III shows these values for the various protons of each substrate. The ν_c values of Table III show the effect of the time-averaged orientation of the cyclohexenones in the cavities of the CDs. As observed with other substrates, the transfer from bulk water to a CD cavity induces normally downfield shifts[13,14] which are more pronounced for α- than for β-CD.[15] Moreover, the shift changes are less pronounced for protons bound at C_3 and C_6 positions of the enone and in one case (the protons at C_6 of **1b**) an upfield induced shift is observed.

Discussion

Insertion Mode of Cyclohexenones 1 in α- and β-CD. The understanding of the regioselectivity effects observed in the $NaBH_4$ reduction of cyclohexenones 1 in the presence of CDs is obviously related to the definition of the mode of insertion of the substrates in the complexes. Relevant information can be obtained[16] from an analysis of ^1H NMR data of Table III and particularly of the ν_c values of the protons bound to C_2, C_4, and C_6 which are common to all substrates.

In the case of β-CD, the downfield shift of the vinyl proton of **1a** and **1b** is less pronounced (by a factor of 2.7) than the corresponding proton of **1c**. On the other hand the opposite trend is observed for the ν_c values of the C_4 protons: that of **1c** is lower than that of **1a** and **1b**. These values apparently indicate an inversion in the preferential inclusion mode on going from **1a** and **1b** to **1c**. Inspection of molecular models clearly indicate that, in the case of **1c**, due to the steric requirements of three methyl groups, insertion of the carbonyl group within the cavity is quite likely the only allowed or highly preferential mode of insertion (mode B). Model A would then be the preferred



geometry for the β-CD complexes with **1a** and **1b**. The ν_c values for the protons at C_6 are difficult to explain and likely related to subtle changes in the electronic distribution of the conjugated enone system.[17] The upfield shift in the case of **1b** could indicate a bent A type penetration (to allow for a deeper insertion of the methyl group at C_3 and somewhat related to the "meta" effect[3a] in the insertion of the phenyl derivatives) which would expose the C_6 methylene to the rim toward bulk solution.

In the case of α-CD all protons with the exception of the vinyl protons at C_2 are strongly shifted downfield without any definite trend. The increase of ν_c for the C_2 protons, on the other hand, based on the above assumptions would indicate a shift from mode A to mode B insertion on going from **1a** to **1b** and **1c**. On the whole in the case of α-CD there seem to be a more random penetration, mode A and B being probably two among other possible ways of insertion.

Thus the indication for the *preferential* insertion modes are the following: mode A for **1a** with both CDs, mode A for **1b** with β-CD and possibly mode B with α-CD, and mode B for **1c** with both CDs. Preliminary data obtained in a parallel investigation[18] of induced circular dichroism for cyclohexenones complexes with CDs confirm the above indications.

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(14) Bergeron, R. J.; Channing, M. A.; McGovern, K. A. *J. Am. Chem. Soc.* **1978**, *100*, 2878.
(15) Bergeron, R.; Rowan, R., III. *Bioorg. Chem.* **1976**, *5*, 425.
(16) For a full discussion of the effects of cycloamyloses on the ^1H NMR spectra of a variety of substrates, see: Bergeron, R. J. In "Inclusion Compounds"; Atwood, J. L., Davies, J. E. D., Mac Nicol, D. D., Eds.; Academic Press: London, 1984; Vol. 3.
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(18) Bonora, G. M.; Fornasier, R.; Scrimin, P.; Tonellato, U. *Carbohydr. Res.*, in press.

In the case of *p*-nitrophenols, the NMR analysis of the inclusion complexes indicates[13] that mode A type insertion, the nitro group inside, is the only preferential mode: the solvation requirements of the OH group, stronger than those of the carbonyl group of enones **1**, apparently prevents its penetration into the cavity. Accordingly, no binding was observed in the case of 3,5-dimethyl-4-nitrophenol due to steric hindrance for a mode A type insertion.[13] This strengthens the assumption of mode B inclusion in the case of **1c**.

Selectivity Effects in the $NaBH_4$ Reduction of Cyclohexenones 1 in the Presence of CDs. The cyclohexanol/cyclohexenol ratios of Table I show that in the case of **1a** with both CDs and of **1b** with β-CD the hydride attack at the double bond is favoured and in the case of **1c** with both CDs and **1b** with α-CD the attack at the carbonyl is preferred on going from bulk water to CDs. Under the above assumption concerning the insertion modes, the hydride attack is enhanced at the carbon atom which is more deeply inserted into the cavity. This would lead to the suggestion that the formation of a ternary complex, where a boron hydride anion[19] and the substrate are included in the CD's cavities, is responsible for the selectivity effects. Unlikely as it may appear, the inclusion of anions into cyclodextrins has been demonstrated and suggestive evidence of the formation of ternary complexes made of CDs, neutral substrates, and inorganic anions has been reported.[20]

On the other hand, the idea of a ternary complex is further supported by the following arguments: (1) The selectivity effects are larger in the case of β- than in that of α-CD. In the latter CD's cavity there is less room to accomodate both the substrate and the anion and, also, the mode of insertion of the substrates is apparently random as compared with that in β-CD. Such a trend was also observed by Komiyama and Hirai in the selective formylation[7b] and carboxylation[7c] of phenols involving the formation of a ternary complex including $:CCl_2$ or CCl_3^+. (2) The effect of modified β-CDs in the reduction of **1b** is less pronounced than that observed with native β-CD. Again this may be due to a decrease in space since the substituents at the 6 position of the glucose units tend to penetrate into the CD's cavity as suggested by Breslow.[21] (3) Most important, although limited to **1b** and β-CD, the kinetic experiments indicated the overall reduction and more specifically the double bond attack is accelerated in the complex. If the hydrides were to be excluded from the inclusion complex an overall retardation and more specifically a more pronounced inhibition of the attack at C_3 would be expected.

Conclusions

The selectivity effects here observed are rather modest as compared with other procedures.[22] The above cited formylations and carboxylations of phenols[7b,c] were reported to occur with selectivities as high as 100%. This excellent goal is the result of a drastic inhibition of the attack at one of the two possible reaction positions and of a slight acceleration or even inhibition of the attack at the other center. The opposite is here observed: None of the possible modes of attack is retarded and one is accelerated (by a factor of 9.5 in the case of **1b** and β-CD); as a consequence, the selectivity effects are less spectacular although the overall rate of the process is enhanced.

The present results point to a large flexibility and to a high degree of unpredictability of the reactivity of cyclodextrin complexes. The insertion mode is a key feature in determining the selectivity effects; from the present results it appears also that maximum filling of the receptor cavity including also hydrophilic reagents should be considered for the reactivity effects.

Experimental Section

^1H and ^{13}C NMR spectra were recorded on a 200-MHz Bruker WP-200 SY spectrometer. Gas chromatography was performed on a Varian 3700 Model instrument using a UCON LB 1715 10% on 80/100 mesh chromosorb WAW-DMCS column.

2-Cyclohexenone (**1a**), 3-methyl-2-cyclohexenone (**1b**), and 3,5,5-trimethyl-2-cyclohexenone (**1c**) were commercial products (Aldrich) distilled before use. α- and β-CD were obtained from Sigma and used without further purification. Heptakis(2,6-*O*-methyl)-β-CD was synthetized according to a reported procedure.[23]

Heptakis(6-*N*-methyl-*N*-acetyl)-β-CD. Heptakis(6-*N*-methyl)-β-CD (1.6 g), obtained according to Breslow's procedure,[21] were dissolved in dry methanol (30 mL). Acetic anhydride (4.72 mL) was then added at once and the solution stirred at room temperature overnight. The solvent was then stripped under reduced pressure and the solid obtained eluted over SiO_2 (5:1, $MeOH/CHCl_3$). Solvent evaporation of the proper fractions afforded heptakis(6-*N*-methyl-*N*-acetyl)-β-CD (1.62 g, 83%) as a white cristalline solid: IR (KBr) 3400 (br), 1640 cm^{-1}; ^{13}C NMR (D_2O)[25] 21.5 (CH_3CO), 35.5, 39.1 (NCH_3), 52.2, 60.0 (C_6), 70.2, 72.5, 73.2 (C_5,C_2,C_3), 82.6 (C_4), 101.9 (C_1), 174.3 (CO) ppm. Anal. Calcd for $(C_9H_{15}NO_5)_7{\cdot}7H_2O$: C, 45.96; H, 7.23; N, 5.96. Found: C, 45.37; H, 6.86; N, 5.65.

General Procedure for Cyclohexenone Reduction. The cyclohexenone (**1a,b**, 0.045 mmol; **1c**, 0.02 mmol) and different amounts of CDs were dissolved in 20 mL of 0.2 M Na_2CO_3. $NaBH_4$ (0.13 mmol for **1a,b** and 0.39 mmol for **1c**) was added and the solution stirred at 25 °C for 3 days. The reaction mixture was then thoroughly extracted with diethyl ether (4 × 7 mL) and the organic layer subjected to VPC analysis. Conversion was ≥98% for **1a,b** and ca. 10% for **1c**.[24] The composition of the diastereomeric cyclohexanols (**2**) mixture was not determined.

Kinetics. The kinetic experiments were performed at 25 °C by withdrawing, at appropriate time intervals, 2 mL aliquots of a 0.2 M solution of Na_2CO_3 containing, at the beginning of the experiment **1b** (0.045 mmol), $NaBH_4$ (0.13 mmol) and, when present, β-CD (0.32 mmol). After the mixture had been extracted with ethyl ether, 1 mL of a 2.36×10^{-3} M ethereal solution of *n*-tetradecane was added (internal standard) and the extracts subjected to VPC analysis.

^1H NMR Measurements. α- and β-CD were dried under vacuum at 80 °C over P_2O_5 for 12 h before preparing the D_2O solutions. The concentrations of substrates, CD, and Me_2SO (used as the internal standard) are in the order of 10^{-3}–10^{-4} M. Each measurement (at 25 °C) is the result of at least 500 scans. As the variation of the experimental chemical shifts is in most cases of a few Hz only, the measurement accuracy was to be held within 0.1 Hz. The binding constants reported in Table III are the average of the values obtained following different resonances, with the exclusion of those resonances varying in a very small range. With the mean K_b value at hand, a set of ν^{calc} values are obtained

(19) The mechanistic details and the nature of the reducing agents in $NaBH_4$ reductions are still to be defined; besides BH_4^-, species like $(OH)BH_3^-$, $(OH)_2BH_2^-$, etc. may be involved. Review: Wigfield, D. C. *Tetrahedron* **1979**, *35*, 415.

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(24) Since the reduction of **1c** is very slow, $NaBH_4$ decomposes completely before total conversion. We did not add more hydride because this could alter the product ratio.[9]

(25) The proton noise decoupled ^{13}C spectrum displays broad bands, deriving from the presence of many nearly resonating carbons. We think that this originates by the probabilistic distribution of the s-*E* and s-*Z* isomers of the amidic functionality. The presence of both isomeric amidic substituents is signalled by the two different *N*-methyl and C_6 resonances.

from equation: $v^{calc} = [CD\cdot1]\ v_c/[1]_0$, while in turn the concentrations of the complex, [CD·1], are calculated from formula 5a in the appendix. The best v_c values are those which minimize the error square function $U = \sum_i (v_i - v_i^{calcd})^2$ and are found through repeated parabolic interpolation.

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Appendix

Derivation of Equation 2. The kinetic expressions for the formation of 2 and 3 from free (1) and complexed (CD·1) substrates are

$$v_i = k_i^f[1] + k_i[CD\cdot1] \qquad (i = 2, 3) \qquad (1a)$$

and may be rearranged to

$$v_i = k_i^f[1]_0 + \Delta k_i[CD\cdot1] \qquad (2a)$$

where $\Delta k_i = k_i - k_i^f$. Under the assumption that the ratio between v_2 and v_3 does not change significantly during the greatest part of the reaction period (which has been verified in the case of the reduction of **1b**), the ratio v_2/v_3 is also the product ratio [2]/[3].

Derivation of Equation 3. For the generic complexation equilibrium

$$1 + CD \rightleftharpoons CD\cdot1 \qquad (3a)$$

with binding constant K_b, the chemical shift of any substrate signal is given by

$$v = v_0[1]/[1]_0 + v_c[CD\cdot1]/[1]_0 \qquad (4a)$$

which reduces to the second term in the second member when the shifts are referred to the measure taken in water, v_0. When the smallest $[CD]_0$ is $\geq 10[1]_0$, the constant reduces to

$$K_b = [CD\cdot1]/\{([1]_0 - [CD\cdot1])[CD]_0\} \qquad (5a)$$

Substitution in (4a) gives (3).

Registry No. **1a**, 930-68-7; **1b**, 1193-18-6; **1c**, 78-59-1; **2a**, 108-93-0; *cis*-**2b**, 5454-79-5; *trans*-**2b**, 7443-55-2; *cis*-**2c**, 933-48-2; *trans*-**2c**, 767-54-4; **3a**, 822-67-3; **3b**, 21378-21-2; **3c**, 470-99-5; heptakis(2,6-*O*-methyl)-β-CD, 51166-71-3; α-CD, 10016-20-3; β-CD, 7585-39-9; heptakis(6-*N*-methyl)-β-CD, 55137-65-0; heptakis(6-*N*-methyl-*N*-acetyl)-β-CD, 99965-65-8.

Resolution and Absolute Configuration of K-Region Trans Dihydrodiols from Polycyclic Aromatic Hydrocarbons

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K-region trans dihydrodiols of benzo[*c*]phenanthrene, chrysene, pyrene, and dibenz[*c*,*h*]acridine have been resolved as their diastereomeric diesters with (−)-(menthyloxy)acetic acid, and their absolute configurations have been assigned by the application of circular dichroism and exciton chirality methods. For these as well as the K-region trans dihydrodiol derivatives from five other hydrocarbons, a consistent pattern of physical properties has emerged. The *R*,*R* diastereomers are less retained on silica gel HPLC columns when eluted with ether–cyclohexane mixtures and show negative values of $[\alpha]_D$ in tetrahydrofuran, the degree of magnetic nonequivalence between H_A and H_B in the $-OCH_AH_BCO_2-$ portion of the diesters (100 MHz, C_6D_6) is generally much higher for the *S*,*S* enantiomers of the dihydrodiols, and the free *R*,*R* dihydrodiols have positive values of $[\alpha]_D$ in tetrahydrofuran provided their hydroxyl groups do not have a marked preference for the pseudodiaxial conformation.

Cytochrome P450 catalyzed formation of K-region arene oxides represents a common pathway in the metabolism of polycyclic aromatic hydrocarbons in mammals. With liver microsomes from 3-methylcholanthrene treated rats, K-region trans dihydrodiols formed by the subsequent action of microsomal epoxide hydrolase on these arene oxides often represent major metabolites: benzo[*e*]pyrene (34%), benz[*a*]anthracene (42%), phenanthrene (69%), and benzo[*c*]phenanthrene (89%).[1] The absolute configuration of these K-region dihydrodiols is of considerable interest from the standpoint of the stereospecificity of the cytochromes P450 which form their precursor arene oxides,[2] of the regiospecificity of epoxide hydrolase in their conversion to dihydrodiols,[3] and of the mechanism of their conjugation with glucuronic acid.[4] To date, only phenanthrene 9,10-dihydrodiol has been assigned absolute configuration directly by chemical correlation with tartaric acid.[5] Subsequently, benzo[*a*]pyrene 4,5-dihydrodiol (after reduction of the chromophore) was assigned[6] through application of an exciton chirality experiment.[7] Assignments of the phenanthrene 9,10-dihydrodiol (a bridged biphenyl chromophore whose conformationally dependent CD spectrum is related to its helicity)[8-10] and the benzo[*a*]-

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